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Effect of istradefylline on mood disorders in Parkinson's disease

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ABSTRACT

Depression is the most common psychiatric complication in patients with Parkinson's disease (PD). Istradefylline, a new anti-parkinsonian agent with completely different mechanism, improves depression-like symptoms in an experimental disease model; however, there is no report of its effects in PD patients. In this study, the effectiveness of istradefylline for treatment of mood disorders in patients with PD was examined in an open-label trial. Thirty PD patients were enrolled. All patients had scores of higher than cut-off level in at least one of the following batteries: Snaith-Hamilton Pleasure Scale Japanese version (SHAPS-J), Apathy scale, or Beck Depression Inventory-2nd edition (BDI). Following study enrollment, all patients received 20 mg of istradefylline, and the dose was increased to 40 mg after 4 weeks. Results from these 3 batteries and the Unified Parkinson's Disease Rating Scale (UPDRS) score were assessed every 2–4 weeks until 12 weeks and the changes in these scores were analyzed. Following administration of istradefylline, the scores of SHAPS-J, Apathy scale, and BDI were significantly improved over time. Significant improvement was also found in the UPDRS score; however, no significant correlation was observed between the score change in these 3 batteries and UPDRS motor function. This is the first study to show the effectiveness of istradefylline for treatment of mood disorders in PD independent of improvement of parkinsonian motor symptoms. In the future, this should be confirmed in a double-blind placebo-controlled trial.

1. Introduction

Parkinson's disease (PD) is a disorder characterized by both motor and non-motor symptoms, such as psychosis, apathy, anxiety, and depression [1]. The manifestation of several non-motor symptoms is thought to be linked to the pathophysiology of PD itself [2]. Depression is the most common psychiatric complication of PD, with a prevalence of 35% in patients with PD according to a recent review [3]. The key characteristic of depression in patients with PD is loss of interest/pleasure [4], which is called anhedonia or apathy. Although there is debate as to whether the symptoms of depression and apathy observed in patients with PD have the same causal mechanism as the disease, reports have suggested that these may be entirely separate entities from the disease process [5]. Similar to apathy, it has been reported that anhedonia should be considered as distinct from depression in patients with PD. [6] Apathy is considered to include several distinct processes that concern with the prefrontal-basal ganglia system, and one of these processes is closely linked to anhedonia. [7–9] As a mechanism of depression, disconnection of functional networks related to amygdala, which is the primary affeted portion in PD, [10] is considered [11] [12] [13].

The impact of mood disorders is an important consideration for patients with PD. The development of apathy after deep brain stimulation of the subthalamic nucleus can cancel the benefits of motor improvements on health-related quality of life (QoL) [14]. Moreover, it was reported depression, measured by the Beck Depression Inventory 2nd edition (BDI) [15], was the most significant predictor of variability in health-related QoL [16]. Thus, treatment of mood disorders is very important in patients with PD.

Recently, istradefylline, which is an adenosine A_{2A} receptor

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antagonist, has been used for treatment of motor symptoms, by a novel mechanism, in patients with PD. [17] To date, there are 4 known types of adenosine receptors. In the brain, the A_{2A} receptor is highly expressed in medium spiny neurons expressing GABA/enkephalin, which comprise the indirect pathway of the basal ganglia, including the striatum and globus pallidus [18]. Adenosine A_{2A} receptor activation in the striatum and external globus pallidus increases the excitability of the GABAergic striato-external pallidal output neurons [19]. Therefore, blockade of these receptors would result in decreased activation of the striato-external pallidal output pathway, restoring the balance in the basal ganglia-thalamocortical circuit and providing an alternative, non-dopaminergic approach to symptomatic relief of PD. This agent modifies dopamine neurotransmission and is used for the treatment of the "wearing-off" symptoms of levodopa in PD [17].

In a previous study, adenosine A_{2A} receptor knockout mice showed significant improvement in the tail suspension test and forced swim test, which suggests an antidepressant effect [20]. Istradefylline improved performance in the forced swim test to the same degree as imipramine, a tricyclic antidepressant drug [21]. Furthermore, in a study with an experimental model of learned helplessness (state do not respond and/or do not try to escape a stressor after long-term exposure to stress), which is a well-established animal model of depressive-like behavior [22], istradefylline improved symptoms of learned helplessness, and this effect was mediated by the adenosine A_{2A} receptor of the nucleus accumbens [23].

It has been established that dopaminergic treatment improves depression in patients with PD [24], and improvement of mood disorders, in general, by anti-parkinsonian agents with different mechanisms-of-action, such as istradefylline, may provide additional benefits. However, there have been no reports on the effectiveness of istradefylline in patients with PD. Therefore, we examined whether this drug improves mood disorders in patients with PD in an open-label trial.

2. Material and methods

2.1. Design

This open-label study was conducted in 6 neurological centers (Juntendo University Hospital, Nippon Medical School Main Hospital, Showa University Hospital, Toho University Omori Medical Center, Tokyo Metropolitan Geriatric Hospital, and The University of Tokyo Hospital) between November 2016 and June 2018. This study was approved by the ethics committees of all participating institutes.

2.2. Patients

We selected patients who fulfilled the criteria of the Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD [25], whose scores were 23 or more on the validated Japanese version of the mini-mental state examination (MMSE) [26], who were nonsmokers, and who were not currently using ketoconazole, rifampicin, midazolam, atorvastatin calcium hydrate, or digoxin. Furthermore, all participants were not using anti-depressants and had scores higher than the cut-off level in at least one of the following batteries: the Snaith-Hamilton Pleasure Scale Japanese version (SHAPS-J) [27], Apathy Scale [28], or BDI.

Patients with scores of 22 or less on MMSE were excluded due to concerns regarding their comprehension of the questionnaires. The reason for excluding smokers and restricting internal medicine is that both smoking and use of these agents may increase the blood concentration of isradifylline. The SHAPS-J, Apathy Scale, and BDI were used to evaluate symptoms of anhedonia, apathy, and depression, respectively. SHAPS-J is a Likert scale self-report questionnaire (range: 0–14). Patients with 3 points or more were classified as having anhedonia. The SHAPS-J was validated [27]. The Apathy Scale with some modifications consists of 14 items scored on a four-point Likert scale. Each score ranges from 0 to 42, with higher scores indicating more severe apathy [28]. A validated Japanese version was also provided. The cut-off score was set at 16/17. The BDI includes a 21-item self-report questionnaire (range, 0–60); the Japanese version of the BDI has also been validated. As per previous recommendations [29], the cut-off score was set at 13/14 in patients with PD, and scores of 14 or more were indicative of depression.

Finally, a total of 30 outpatients with PD were enrolled in this study. Written informed consent was obtained from all patients.

2.3. Procedures

At initial assessment, we checked not only Hoehn and Yahr (HY) scale and Unified Parkinson's Disease Rating Scale (UPDRS) part I, II (on time), III, and IV scores, but also daily levodopa dose and levodopa equivalent dose (LED). LED was determined according to previously described methods [30]. Change in daily medication was not allowed in this study.

After patients were selected, all were administered 20 mg istradefylline (NOURIAST® 20 mg tablet, Kyowa Hakko Kirin, Tokyo, Japan) every morning with other daily medications. After 4 weeks, the daily dose of istradefylline was increased to 40 mg.

The SHAPS-J, Apathy Scale, and BDI scores were assessed after the 2nd, 4th, 8th, and 12th week. UPDRS part I, II (on time), III, and IV scores were checked after the 2nd, 8th, and 12th week. Then, we assessed the score change over time ((score of each observed week) - (baseline score)) and the score changing ratio (%: [(score of each observed week) - (baseline score)]*100 / (baseline score)) of the SHAPS-J, Apathy Scale and BDI after initiation of istradefylline treatment. The score change of the UPDRS over time was also checked. To evaluate whether mood changes were correlated with changes in UPDRS score, we assessed the correlation of the score changing ratio, from baseline to the 12th week, between each questionnaire and UPDRS.

Paired *t*-tests were used to evaluate the score change and the score changing ratio of SHAPS-J, Apathy Scale, BDI and UPDRS scores. The correlation between score changes in the mood evaluation questionnaires and UPDRS was evaluated by Pearson's correlation coefficient. Statistical calculations were performed using JMP (version 11 for Macintosh software; SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $p < .05$. All data are presented as mean ± standard deviation.

3. Results

The analysis was performed on a total of 30 patients with PD; however, 5 patients dropped out at the end of the 4th week due to changes in physical condition unrelated to PD in two, pneumonia in one, deterioration of dyskinesia in one, and femoral shaft fracture in one. The profile of the enrolled patients is shown in Table 1. Baseline scores for the SHAPS-J, Apathy Scale, and BDI were above the cut-off for 14, 24, and 27 patients, respectively. Some patients were included in > 2 groups. The profile of these patients group is also shown in Table 1.

Istradefylline was safe and well tolerated.

3.1. Analysis of SHAPS-J

Following administration of istradefylline, SHAPS-J scores were significantly reduced from baseline at 4, 8, and 12 weeks ($p = .01$, 0.04 and 0.003, respectively; see Table 2A). The mean of the score reduction ratios (i.e. the score changing ratio from baseline) linearly improved time passed, and the score changing ratios at the 4th, 8th, and 12th week were significantly improved compared to baseline (see Fig. 1A). At the end of 12th week, the mean of the score changing ratio of the SHAPS-J was about −50% from baseline (see Fig. 1A). Significant improvement was also found in the UPDRS part I, part II, part III, and

Table 1
Table 1: Characteristics of the patients with PD enrolled in the study. SHAPS-J, Snaith-Hamilton Pleasure Scale Japanese version; BDI, Beck Depression Inventory-2nd edition; LED, levodopa equivalent dose; MMSE, mini-mental state examination.

	total	Patients group		
		SHAPS-J ≥ 3	Apathy Scale ≥16	BDI ≥ 14
n (male / female) at base	30 (10 / 20)	14 (5 / 9)	24 (7/ 17)	27 (8/ 19)
age (years old)	71.2 ± 9.8	73.0 ± 11.4	71.1 ± 10.1	71.3 ± 10.3
disease duration (years)	6.4 ± 4.7	6.8 ± 4.0	6.4 ± 4.8	6.5 ± 4.9
modified Hoehn-Yahr stage	2.8 ± 0.5	2.6 ± 0.5	2.7 ± 0.5	2.7 ± 0.5
daily levodopa dose (mg)	365.5 ± 134.4	371.4 ± 115.5	334.7 ± 115.2	365.4 ± 129.4
daily LED	543.2 ± 236.4	491.0 ± 203.4	474.0 ± 165.9	535.4 ± 235.6
MMSE	28.0 ± 2.2	27.9 ± 1.9	28.0 ± 2.3	28.1 ± 2.2

part I-III total scores (see Table 2A). No significant correlations were observed between the score change of the SHAPS-J and the UPDRS at the 12th weeks (see Table 3).

3.2. Analysis of apathy scale

The Apathy scale score was also significantly reduced from baseline at the 2nd, 4th, 8th, and 12th week after commencement of istradefylline treatment (p = .02, 0.05, 0.01, and 0.005, respectively; see Table 2B). The mean of the score reduction ratio at the 2nd, 4th, 8th, and 12th week were also significantly improved compared to baseline (see Fig. 1B). This ratio rapidly improved at 2 weeks, by −11%, and subsequently plateaued. Significant improvement was also seen in the UPDRS part I, part III, and part I-III total scores (see Table 2B). Significant correlation was observed between the Apathy Scale and UPDRS part I scores at the 12th week (see Table 3).

3.3. Analysis of BDI

The BDI score was also significantly improved from baseline at the 2nd, 4th, 8th, and 12th week following commencement of istradefylline treatment (p = .0001, 0.03, 0.02, and 0.0001, respectively; see Table 2C). The mean of the score reduction ratios at 2, 8, and 12 weeks were also significantly improved compared to baseline (see Fig. 1C). This ratio improved at 2 week by about −20%, and then, following one fluctuation, improved to −30% at 12 weeks. Significant improvement was also found in the UPDRS part I, part III, and part I-III total scores (see Table 2C). Significant correlation was observed between BDI and UPDRS part I only at 12 weeks (see Table 3).

4. Discussion

In this study, significant score improvement was observed in SHAPS-J, Apathy scale, and BDI score upon istradefylline treatment in

Table 2
Score change after administration of istradefylline for each scale. (A) SHAPS-J, (B) Apathy scale, and (C) BDI SHAPS-J, Snaith-Hamilton Pleasure Scale Japanese version; BDI, Beck Depression Inventory-2nd edition; UPDRS, Unified Parkinson's Disease Rating Scale; a, < 0.001; b, < 0.01; c, < 0.05.

A.

		SHAPS-J	UPDRS				
	n		part I	part II on	part III	part I-III total	part IV
Baseline	14	3.9 ± 1.2	2.9 ± 1.2	11.0 ± 7.8	15.9 ± 5.9	29.7 ± 11.7	2.1 ± 1.7
The 2nd week	14	3.2 ± 1.5					
The 4th week	14	2.9 ± 1.1[c]	2.1 ± 0.9[c]	9.5 ± 6.1	13.4 ± 5.0[c]	25.1 ± 9.9[b]	1.9 ± 1.4
The 8th week	13	2.5 ± 2.4[c]	1.9 ± 1.0[c]	8.6 ± 5.8[c]	13.3 ± 5.1[c]	23.8 ± 9.1[a]	1.7 ± 1.3
The 12th week	13	2.2 ± 1.9[b]	1.9 ± 1.3[c]	9.1 ± 6.0[c]	11.8 ± 4.4[b]	22.8 ± 9.8[a]	1.7 ± 1.4

B.

		Apathy Scale	UPDRS				
	n		part I	part II on	part III	part I-III total	part IV
baseline	24	22.8 ± 5.0	2.8 ± 1.3	9.5 ± 5.5	17.1 ± 7.2	29.3 ± 10.6	3.5 ± 1.4
The 2nd week	24	20.3 ± 6.3[a]					
The 4th week	24	20.3 ± 6.3[c]	2.4 ± 1.2[c]	9.9 ± 5.6	14.7 ± 6.8[b]	27.0 ± 10.6[b]	2.0 ± 1.8
The 8th week	22	20.2 ± 6.4[b]	2.1 ± 1.4[b]	8.5 ± 4.8	14.0 ± 7.1[b]	24.7 ± 10.6[a]	2.1 ± 2.4
The 12th week	22	19.6 ± 6.7[b]	2.2 ± 1.6[c]	9.7 ± 5.6	13.0 ± 7.1[a]	24.9 ± 11.8[a]	2.0 ± 2.2

C.

		BDI-II	UPDRS				
	n		part I	part II on	part III	part I-III total	part IV
baseline	27	20.6 ± 6.9	2.6 ± 1.6	10.1 ± 6.4	16.6 ± 7.7	29.3 ± 13.1	3.3 ± 6.4
The 2nd week	27	16.6 ± 6.8[a]					
The 4th week	27	17.5 ± 6.2[c]	2.2 ± 1.5[c]	10.5 ± 6.4	14.0 ± 7.2[a]	26.7 ± 12.4[b]	1.9 ± 1.6
The 8th week	23	16.4 ± 7.9[b]	1.9 ± 1.5[b]	8.4 ± 5.0	13.0 ± 6.8[b]	23.2 ± 10.3[a]	2.0 ± 2.3
The 12th week	23	14.3 ± 7.3[a]	1.9 ± 1.6[c]	9.6 ± 5.8	12.3 ± 6.3[a]	23.8 ± 10.9[b]	1.9 ± 2.2

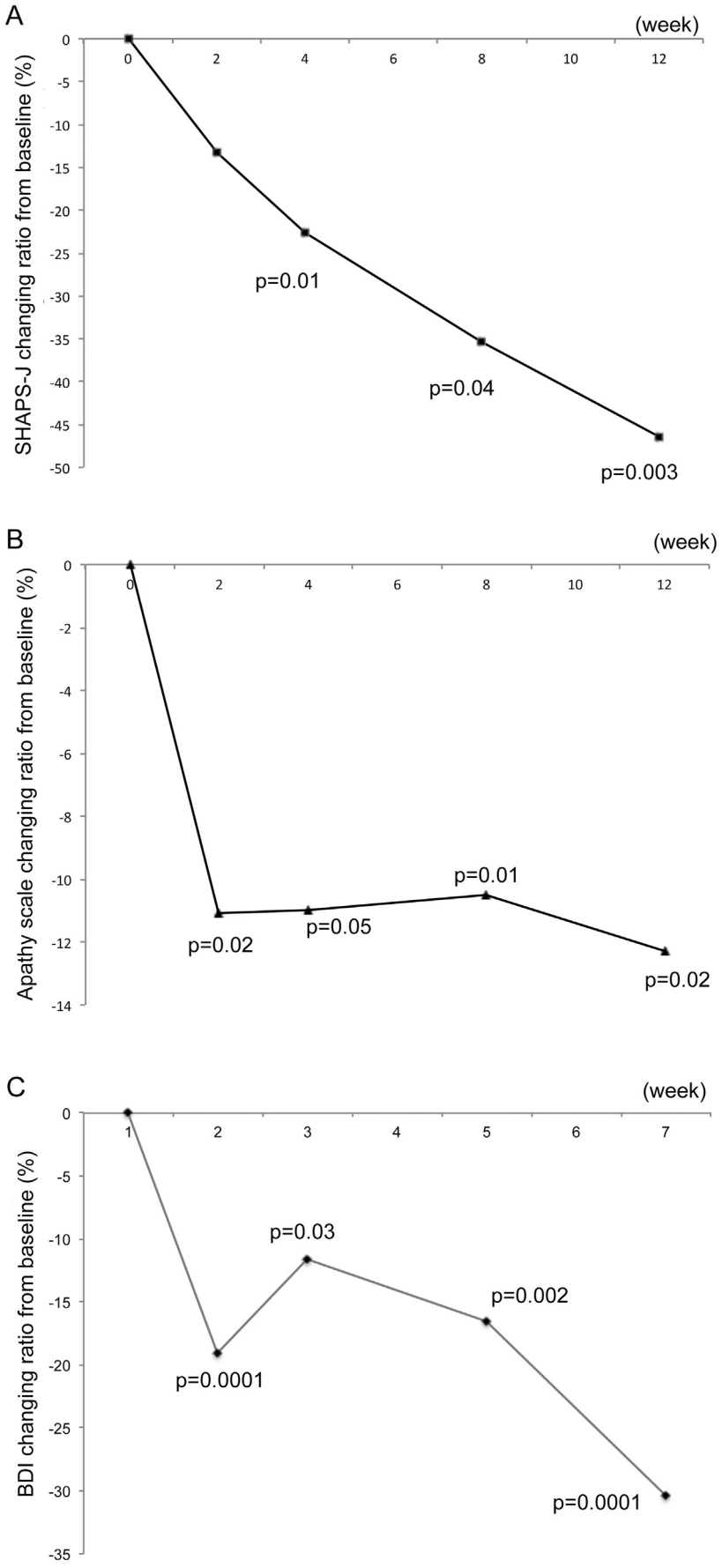

Fig. 1. Score changing ratio from baseline. (A) SHAPS-J, (B) Apathy scale, and (C) BDI Changing ratio (%) was calculated as below: [(score of each observed week) - (baseline score)]*100/(baseline score). If a statistically significance difference between a score and baseline was found, the *p* value is shown. NS, not significant.

Table 3
Correlation between the score change for each scale and the UPDRS scale at the 12th week. Score change was calculated as below: (score of each observed week) - (baseline score); *r*, Pearson's correlation coefficient; SHAPS-J, Snaith-Hamilton Pleasure Scale Japanese version; BDI, Beck Depression Inventory-2nd edition; UPDRS, Unified Parkinson's Disease Rating Scale; NS, not significant.

	UPDRS part I		UPDRS part II on		UPDRS part III	
	r	*p value*	*r*	*p value*	*r*	*p value*
SHAPS-J	0.50	0.10 (NS)	−0.42	0.18 (NS)	−0.22	0.50 (NS)
Apathy scale	0.57	0.009	0.17	0.47 (NS)	0.07	0.76 (NS)
BDI	0.58	0.006	0.29	0.20 (NS)	−0.24	0.30 (NS)

patients with PD. Improvement in UPDRS score was also observed upon istradefylline treatment; however, there was no significant correlation between the improvement of mood and parkinsonian motor symptoms. This is the first report showing efficacy of istradefylline for the treatment of PD patients with mood disorders, not dependent on improvement of motor symptoms.

As mentioned above, the core features of depression in PD patients are anhedonia and apathy. Anhedonia is considered to be closely related to apathy, and may be a part of the syndrome of apathy [7], as defined by the criteria of Marin [8]. Apathy may not necessarily be a homogenous entity. Levy and Dubois defined three subtypes of disrupted processing in the prefrontal-basal ganglia system as possible morphological causes of apathy: emotional-affective processing, cognitive processing, and auto-activation processing [9]. Emotional-affective processing is closely linked to quantitative reduction of voluntary actions. It is associated with loss of interest in daily-life activities, situations, or stimuli that were previously considered to be motivating, which is closely linked to anhedonia. This is believed to be associated with dysfunction in the orbital and medial prefrontal cortex (PFC).

Four frontostriatal loops have been described as modulators of motor and affective function [31]. These loops are affected by dopamine depletion gradients in PD patients, which are larger in the dorsal striatum (motor control) and smaller in the ventral striatum (affective control). As disease progresses, there is dysfunction of a loop comprised of the nucleus accumbens (ventral striatum) and certain areas of the orbitofrontal cortex that is related to affective control. In a shape analysis study using magnetic resonance imaging (MRI), atrophy of the nucleus accumbens was found to be related to apathy in patients with PD. [32] Thus, anhedonia and apathy may be triggered by dysfunction of this affective loop. As described above, istradefylline improved symptoms of learned helplessness in animal models, and this effect is mediated by the adenosine A_{2A} receptor of the nucleus accumbens [23]. Therefore, istradefylline may improve anhedonia and apathy in PD patients through functional modulation of adenosine A_{2A} receptor at the nucleus accumbens.

Depression in PD patients may be related to the pathophysiological mechanism of PD itself. In the amygdala-centric model of major depressive disorder, lesions to the ventromedial PFC, orbital PFC, or basal ganglia may abrogate top-down control of the amygdala and deeper limbic structures. Functional hypersensitivity of deeper limbic structures and/or the amygdala may disrupt prefrontal emotional regulation [33]. Similar to major depressive disorder, recent studies using single-photon emission computed tomography and functional MRI revealed abnormalities in the prefrontal cortex, basal ganglia, limbic system (including the cingulate cortex, thalamus, amygdala, and ventral striatum), and their networks in PD patients with depression [11–13]. Similar to anhedonia and apathy, disruption of the PFC may play an important role in the development of depression in patients with PD. Therefore, istradefylline may improve depression of patients with PD by the same mechanism as its effects on anhedonia and apathy.

Another potential explanation of the effect of istradefylline on anhedonia, apathy, and depression exists. Kadowaki et al. showed istradefylline increased dopamine levels in the PFC in both normal and PFC-lesioned PD model rats treated with 6-hydroxydopamine [34]. The A10 dopaminergic neurons develop in the ventral tegmental area, which is the area primarily affected by lesions in PD. These neurons innervate the nucleus accumbens and PFC via the mesocorticolimbic system, and are involved in regulation of emotion and reward [35]. Thus, increasing dopamine levels in the PFC by istradefylline administration may ameliorate mood disturbances, such as anhedonia, apathy, and depression.

This study had several limitations. The first was that it was an a open-label trial, and there is known to be a large effect of the placebo response in patients with PD. [36] To confirm our findings, our next step will be to design a double-blind placebo-controlled trial. The second limitation was the number of patients recruited and the number that dropped out. Since this was a preliminary trial, the original recruitment number was low. Furthermore, 5 patients were dropped out in this study. As only 30 patients were recruited at the beginning of this study, the dropout rate was about 17%. In a previous study, Richard et al. examined the usefulness of paroxetine and venlafaxine for depression in PD patients [37]. This provided the first class I evidence of the use of selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI) for the treatment of depression in patients with PD. In this study, 195 patients were initially recruited; however, > 40% of initially recruited patients dropped out, leaving only 115 eligible patients. Therefore, the dropout ratio of our study (17%) is not unusually high for trials relating to mood disorders in PD patients.

In conclusion, this study is the first to show the efficacy of istradefylline, which is a new anti-parkinsonian agent with a novel mechanism-of-action, for the treatment of mood disorders in PD patients independent of improvement of motor symptoms. While anhedonia, apathy, and depression may be separate entities from the PD disease process [5,6], it has been suggested that the etiologies of disorders could be linked to the pathophysiology of PD. Therefore, typical anti-parkinsonian treatments may also effective for treatment of these states in PD patients [38]. As SSRIs and SNRIs can exacerbate parkinsonian motor symptoms [39], [40] anti-parkinsonian agents, such as istradefylline, may by the best option for treating PD-associated mood disorders. Our study provides new insights into this treatment avenue.

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